ORIGINAL ARTICLE

Serum PAPP-A and Maternal Risk Factors in Prediction of SGA: A Retrospective Study

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Abstract

Aim: Assess the predictive value of first-trimester serum PAPP-A and maternal risk factors in the occurrence of small for gestational age (SGA) newborn in our local South Asian population.

Materials and methods: Retrospective case series of antenatal women with singleton gestation who underwent the first-trimester combined screening from January 2013 to December 2015 and had regular checkups and delivered with us. The maternal characteristics analyzed include basic demographics, medical history, medication history, obstetric history, and value of PAPP-A MoM. The neonatal outcome analyzed includes gestational age at delivery, and the birth weight of the baby. Women were divided into three groups as low, intermediate, and high risk and outcomes were analyzed. Statistical analysis was done using Fisher's exact test and unpaired *t*-test.

Results: Of the 1,017 antenatal women, 590 met inclusion criteria, of which 40 women delivered SGA, and 550 women delivered non-SGA newborns. Of the 38 antenatal women where PAPP-A MoM ≤ 0.415 MoM, four and 34 delivered SGA, and non-SGA newborns , respectively. Of the 590 women, 507 were low risk, and 77 and six belonged to intermediate and high risk, respectively. 57.14% of the intermediate-risk and 100% in the high-risk group received aspirin. Twelve newborns were SGA in the intermediate-risk and no SGA in the high-risk group. The detection rate for SGA with low PAPP-A in our study was 10%, similar to the study by Nicholaides et al., where the detection rate was 12%.

Conclusion: In the absence of past, current risk factors and a PAPP-A >0.415 MoM, the negative predictive value for SGA was 94.47%.

Clinical significance: Assessment of risk factors for SGA fetus at booking helps to provide the earliest effective intervention for prevention of SGA.

Keywords: Combined screening, Retrospective study, Risk factors, SGA, Singleton.

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Introduction

Small for gestational age is associated with increased morbidity and mortality in the perinatal period.[1,2] Prematurity and low birth weight account for 20% of neonatal mortality in South India.[3] SGA is defined as a neonate with a birth weight of less than the 10th percentile for gestational age.

PAPP-A is secreted by syncytiotrophoblast and can be detected in maternal serum, placental tissue, and amniotic fluid. PAPP-A is an enzyme that divides insulin-like growth factor binding protein (IGFBP)— 4 and 5, hence increasing the bioavailability of insulin-like growth factors necessary for fetal growth.[4] PAPP-A levels represent placental function; low PAPP-A levels result in SGA infants by decreasing the availability of nutrients to chorionic villi.[5] A low level (</= 0.415 MoM) of the first-trimester marker PAPP–A is a major risk factor for delivery of an SGA neonate.[6]

Small for gestational age may be due to a constitutionally small fetus or nonplacental mediated growth restriction like a structural or chromosomal anomaly, metabolic disorders, and fetal infection or placental mediated growth restriction. Maternal factors like low prepregnancy weight, undernutrition, substance abuse, and preexisting medical conditions like severe anemia, preeclampsia, autoimmune disease, thrombophilias, renal disease, diabetes, and essential hypertension can affect placental implantation, vasculature and hence the transfer of nutrients.

Prediction of SGA by first-trimester identification of risk factors is beneficial as early intervention with low dose aspirin can prevent SGA [NNT- 71 for IUGR,[7] NNTB -146 and the baby being born SGA (seven fewer per 1000 treated)].[8]

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The aim of the study is to assess the predictive value of first-trimester serum PAPP-A and maternal risk factors in the occurrence of SGA newborns in our local South Asian population.

Materials and Methods

Retrospective case series of all antenatal women with singleton gestation who underwent first-trimester screening (11–13 + 6 weeks) for aneuploidies at the Institute of Reproductive Medicine, Madras Medical Mission, and had regular antenatal follow ups and delivered with us were included in the study.

Women who had multiple pregnancies declined combined screening or delivered elsewhere were excluded.

All first-trimester bookers were offered first-trimester screening (11–13 + 6 weeks) for trisomies with nuchal translucency and double marker testing. Scan was performed at 11–13 + 6 weeks when fetal

CRL is between 45 and 84 mm for nuchal translucency and nasal bone. All women received pretest and posttest counseling by the respective obstetricians and information leaflets.

Blood samples were collected on the same day of the scan and sent for serum beta human chorionic gonadotropin (HCG) and PAPP-A to a single outsourced lab. All relevant maternal and scan details were documented in the test request to be incorporated in the result analysis. Samples were analyzed in a single lab by solid-phase enzyme-labeled chemiluminescence competitive immunoassay technique. PRISCA software was used for the calculation of MoM.

All antenatal women were followed up with routine care with growth scans at 26–30 and 33–37 weeks, and frequently follow up of certain women were done based on risk factors. The mode of delivery was based on the obstetric indication.

Records were reviewed for the period between January 2013 and December 2015.

Data on maternal characteristics and neonatal outcomes were collected from the birth register, clinical records, and electronic summaries. The maternal characteristics analyzed include basic demographics, medical history, medication history, obstetric history, and value of pregnancy-associated plasma protein-A in MoM. The neonatal outcome analyzed includes gestational age at delivery, and birth weight of the baby.

Women were divided into three groups as low, intermediate, and high risk, and outcomes were analyzed. Low PAPP-A was defined as </= 0.415 MoM.[6] SGA was defined as <10th centile birth weight for gestational age. Risk factors identified include age >40 years, nulliparity, previous recurrent miscarriages, maternal medical diseases like chronic hypertension, overt diabetes, chronic renal disease, autoimmune disorders, thrombophilia, previous history of abruption, preeclampsia, intrauterine fetal death, prematurity due to placental causes, or low PAPP-A. The low-risk group is where there is normal PAPP-A and no maternal, prior obstetric risk factors for SGA. The intermediate-risk group is where there is either low PAPP-A or maternal, prior obstetric risk factors for SGA. High risk is where there is low PAPP-A and maternal, prior obstetric risk factors for SGA.

The data was entered into an excel spreadsheet. Statistical analysis was done using Fisher's exact test for categorical variables and the unpaired *t*-test for continuous variables.

Results

Of the 1,017 antenatal women who underwent first-trimester screening over 2 years, 65 had twin gestation, 36 women opted out of the combined screening, 20 had anomalies and miscarriages, 306 were delivered elsewhere, and 590 women met inclusion criteria.

Of these 590 women, 40 women delivered SGA, and 550 women delivered non-SGA newborns.

Table 1 shows the maternal characteristics were similar in the SGA and non-SGA groups except for those women with autoimmune disorders where SGA was statistically significant, and the value of PAPP-A was significantly low in the SGA group.

Table 2 shows the occurrence of preeclampsia and preterm delivery due to placenta associated pregnancy complications were significantly high in the SGA group, and the birth weight was significantly lower in the SGA group.

Table 3 shows the different risk groups and their outcome. Of the 590 antenatal women, 507 were low risk, 77 and 6 belonged to intermediate and high risk, respectively.'

There was no SGA in the high-risk group, and 12 newborns were SGA in the intermediate risk group. Of the 38 antenatal women who had PAPP-A MoM </= 0.415 MoM, four delivered SGA, and the detection rate for low PAPP-A was 10%.

Discussion

- Assessment of risk factors for SGA at booking must be individualized considering current and past maternal characteristics, and medical and obstetric history with

Table 1: Comparison of maternal characteristics in SGA and non-SGA groups

	SGA (n = 40)	*Non-SGA (n = 550)*	*p value (<0.05)*
Maternal risk factors			
Average age	30.65	29.54	0.10
Age >40 yrs	1	7	0.43
Nulliparity	20	280	1.00
Previous recurrent miscarriages	4	29	0.27
ART conception	13	132	0.25
Previous pregnancy history			
Past placental causes	2	17	0.37
Past nonplacental causes	1	6	0.39
Maternal medical history			
Chronic medical disease	5	35	0.18
Autoimmune	3	4	0.008[a]
Thrombophilia	1	16	1.00
Current pregnancy			
NT (mm)	1.54 ± 0.35	1.49 ± 0.35	0.42
CRL (mm)	63.53 ± 6.92	63.84 ±6.99	0.78
Mean PAPP-A (MoM)	0.79	1.15	0.002[b]

Fisher's exact test for categorical variables and unpaired *t*-test for continuous variables

Table 2: Comparison of maternal and neonatal outcome in SGA and non-SGA groups

Pregnancy outcome	*SGA (n = 40)*	*Non-SGA (n = 550)*	*p-value (0.05)*
Percentage of women on aspirin	15%	8%	–
Abruption	1	2	0.19
Preeclampsia	4	5	0.001[a]
Gestational hypertension	2	26	1.00
Preterm <37 weeks (<34 weeks)	8(5)	61(14)	0.12
Placental cause	7(4)	3(2)	0.0001[b]
Obstetric cause	1(1)	58(12)	0.165
Gestational age at delivery (weeks)	$37^{+}4$	$38^{+}1$	0.542
Birth weight (kg)	2.188	3.090	0.0001[c]

Fisher's exact test for categorical variables and unpaired *t*-test for continuous variables; Figures within brackets indicate preterm fetuses <34 weeks; [a, b]: Incidence of preeclampsia and placental cause of preterm delivery is significantly higher in the SGA group; [c]: Birth weight is significantly higher in the non-SGA group

Table 3: Outcome in risk groups

Risk groups	*Number of antenatal women*	*No of antenatal women with PAPP-A </= 0.415MoM*	*No of antenatal women with risk factors*	*No of women used aspirin from first- trimester(%)*	*No of women delivered SGA(%)*	*Mean birth weight (kg)*
Low risk	507	–	–	–	28(5.52%)	3.07
Intermediate risk	77	32	45	44(57.14%)	12(15.58%)	2.8
High risk	6	6	6	6(100%)	–	2.82

reassessment at subsequent visits will guide us to provide increased surveillance for the same and hence reduce perinatal morbidity and mortality. Umbilical artery doppler should be the primary surveillance tool in SGA fetuses.[6]

- Use of aspirin at a dose of 75 mg daily started at the latest by 16 weeks and continued till delivery in this study was considered for those women if risk factors for preeclampsia were present and hence 57.14% of women in the intermediate and 100% of women in the high-risk group received aspirin. This intervention might have completely prevented SGA in the high-risk group.

Use of aspirin reduced the overall incidence of SGA <10th, <5th, and <3rd percentiles by 30–40% in babies born at <37 weeks gestation and by about 70% in babies born at <32 weeks; in babies born at ≥37 weeks, aspirin did not have a significant effect on the incidence of SGA. Preterm PE is, to a great extent, predictable by first-trimester combined screening and preventable by the use of 150 mg/day of aspirin from the first to the third trimester. A beneficial consequence of such a strategy in the prevention of a high proportion of cases of preterm SGA because, first, preterm PE is commonly associated with SGA and, second, a high proportion of preterm SGA is associated with PE.[9]

- Due to the retrospective study design and medical intervention to prevent SGA in 57.14% of intermediate and 100% of high-risk antenatal women, there is a limitation in arriving at a positive predictive value for first-trimester serum PAPP-A and maternal risk factors in the occurrence of SGA.
- As not all patients with risk factors for SGA received aspirin, we could not exactly assess the role of aspirin in the prevention of SGA. There is a need for prospective trials in the intermediate-risk group to ascertain the effectiveness of aspirin in the prevention of SGA.
- But in the absence of past and current risk factors for SGA and a PAPP-A value of >0.415 MoM, the negative predictive value for SGA was 94.47%.
- The detection rate (sensitivity) for SGA with low PAPP-A in our study was 10%, similar to the study by Nicholaides et al., where the detection rate was 12%.[6]

Conclusion

If there are no maternal risk factors and PAPP-A is >0.415 MoM, the negative predictive value for SGA is 94.47%.

Assessment of risk factors for SGA fetus at booking helps to provide the earliest effective intervention for prevention of SGA.

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